PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	01.06.2004
Applicant's or agent's file reference N.90066	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 03/07443	12.03.2003	25.03.2002

Applicant
WISCONSIN ALUMNI RESEARCH FOUNDATION

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Senkel, H Tel. +49 89 2399-8071

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference N.90066	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US 03/07443	International filing date *(day/month/year)* 12.03.2003	Priority date *(day/month/year)* 25.03.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/59, A61K31/59		
Applicant WISCONSIN ALUMNI RESEARCH FOUNDATION		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16.10.2003	01.06.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Ansaldo, M Telephone No. +49 89 2399-7876

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US 03/07443

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

2-33	as originally filed
1	received on 20.06.2003 with letter of 22.04.2003

Claims, Numbers

2-28	as originally filed
1	received on 03.03.2004 with letter of 03.03.2004

Drawings, Sheets

1/2-2/2	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-28

   because:

   ☒ the said international application, or the said claims Nos. 1-28 with respect to I.A. relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	11-19,22
	No:	Claims	1-10,20,21,23-28
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-28
Industrial applicability (IA)	Yes:	Claims	-
	No:	Claims	

2. Citations and explanations

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US 03/07443

see separate sheet

Re Item III:

Claims 1-28 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V:

The documents cited in the International Search Report (ISR) are numbered D1-D7 in the order of their listing. Unless otherwise specified, reference is made to the passages cited in the search report.

1. Present claim 1 is not acceptable under Art. 6 PCT. The therapeutic application is functionally defined by a mechanism of action ("stimulating ***osteoblastic-mediated*** growth of new bone") which does not allow any practical application in the form of defined, real treatment of a pathological condition (disease).

2. D1-D3 disclose 2-methylene-19-nor-dihydroxyvitamin D3 for the improvement of bone fracture healing and improved bone grafts.
   D3 in particular discloses that the claimed compound "can also be used in conjunction with bone replacement procedures, such as hip replacements, knee replacements and the like".

   The property of 2-methylene-19-nor-dihydroxyvitamin D3 to stimulate ***osteoblastic-mediated*** growth of new bone does not appear to be a new technical effect deriving from a new use, as 2-carbon-modified analogs of 1,25-$(OH)_2$D3 were already used to increase the rate of skeletal repairs such as repair of fractures and solidification of implants in D1-D3.
   Therefore the subject-matter of claims 1-10,20,23-28 cannot be considered novel over D1-D3 (Art. 33 (1) and (2) PCT).

3. The same applies to D4 and D5, which disclose 2-methyl-19-nor-20(S)-1alpha,25-dihydroxyvitamin D3 for the improvement of bone fracture healing and improved bone grafts and the selective mobilization of calcium from bone.
   D4 and D5 anticipate hereby the subject-matter of claims 1-9,21,23-28 (Art. 33 (1) and (2) PCT).

4. The subject-matter of claims 11-19, 22 referring to the acylated derivatives of formula I, appears to be novel as it is not anticipated by the cited prior art (Art. 33 (1) and (2) PCT).

5. However no inventive step for claims 11-19, 22 can be acknowledged for the following reasons:

D6 discloses derivatives of 1alpha,25-dihydroxyvitamin D3 analogs, in which a hydrolyzable group is attached to the hydroxy group at carbon 25 of the molecule and optionally to any other of the hydroxy groups present in the molecule. The presence of the hydrolyzable group attached to the hydroxy group at carbon 25 of the molecule provides for the "slow release" of the biologically active vitamin D compound. The hydrolyzable group is preferably an acyl group as described on page 6, l.7.

It would be obvious to the person skilled in the art to apply the teaching of D6 with corresponding effect to the compounds disclosed in documents D1-D3, thereby arriving at 2-methylene-19-nor-dihydroxyvitamin D3 acylated derivatives according to claims 11-19, 22.
The subject-matter of claims 11-19, 22 does therefore not involve an inventive step (Article 33(3) PCT).

6. For the assessment of the present claims 1-28 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

USE OF CARBON-2-MODIFIED-19-NOR-VITAMIN D ANALOGS TO INDUCE THE FORMATION OF NEW BONE

BACKGROUND OF THE INVENTION

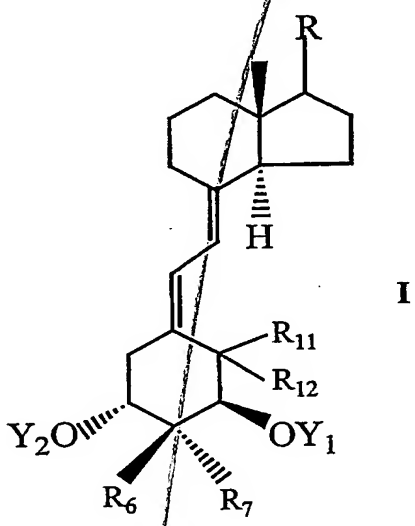
The present invention relates to vitamin D compounds, and more particularly to 19-nor vitamin D compounds substituted at the carbon 2 position which are useful for stimulating growth of new bone.

The ability of vitamin D to bring about normal bone formation is well recognized and has been for well over 75 years. Thus, vitamin D will heal rickets and osteomalacia. In the case of these two diseases, it is envisioned that the osteoblasts of bone are able to synthesize the organic matrix of the skeleton even in the absence of vitamin D but that vitamin D is required for the deposit of mineral in the newly-layed down matrix. In this capacity, it is generally believed that vitamin D heals rickets and osteomalacia by the elevation of plasma calcium and phosphorus to levels required for the mineralization process to proceed (DeLuca[1], 1981). Thus, early work (Shipley, Kramer, and Howland,[2,3] 1925; 1926) suggested that serum taken from normal rats could heal rachitic lesions in culture, whereas serum taken from rachitic rats was unable to bring about the same healing process. Later, it was discovered that this was because vitamin D by virtue of its ability to elevate the absorption of calcium and phosphorus in the small intestine, is able to raise the plasma calcium and phosphorus to supersaturation levels required for the mineralization of the skeleton. Furthermore, it was envisioned that vitamin D also could cause the mobilization of calcium from bone to elevate plasma calcium concentration (DeLuca[1], 1981) or could stimulate the kidney to reabsorb calcium from the formed urine (Yamamoto et al.[4], 1984) raising the plasma calcium and phosphorus product needed for the mineralization process. Final proof that this is the case was provided when calcium and phosphorus infusion into the blood stream

CLAIMS

I claim:

1. A method of stimulating growth of new bone in a mammal comprising administering to a mammal in need thereof a therapeutically effective amount of a compound having the formula:



I

where Y_1 and Y_2, which may be the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group, where R_{11} and R_{12} are each hydrogen or taken together are a methylene group, where R_6 and R_7, which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, fluoroalkyl, hydroxy and alkoxy, with the proviso that R_6 and R_7 cannot both be hydrogen, or R_6 and R_7 when taken together may represent the group $-(CH_2)_x-$ where X is an integer from 2 to 5, or R_6 and R_7 when taken together may represent the group $=CR_8R_9$ where R_8 and R_9, which may be the same or different, are each selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, fluoroalkyl, hydroxy and alkoxy, or when taken together R_8 and R_9 may represent the group $-(CH_2)_x-$ where X is an integer from 2 to 5, and where the group R represents